

Applicants: Kung, *et al.*
U.S.S.N.: 10/590,672

Amendments to the Specification:

Please amend the paragraph beginning on page 22, line 17 as follows:

A cytotoxic agent is any agent that is harmful to cell structure and function, and which may ultimately cause cell death. For example a cytotoxic agent is a chemotherapeutic agent or radiation therapy. A chemotherapeutic agent is any agent that is used to treat cancer. A chemotherapeutic agent includes alkylating agents (e.g., chlorambucil, cyclophosphamide, thiotepa, and busulfan); anti-metabolites agents (e.g., purine antagonists, pyrimidine antagonists, and folate antagonists); mitotic inhibitor such as plant alkaloids (e.g., actinomycin D, doxorubicin, mitomycin, paclitaxel, docetaxel, etoposide (VP-16), vinblastine, vincristine, and vinorelbine); anti-tumor antibiotics (e.g., bleomycin, dactinomycin, daunorubicin, doxorubicin (Adriamycin[®]), idarubicin, and mitoxantrone); proteasome inhibitors (e.g. bortezomib), corticosteroids hormones (e.g., prednisone and dexamethasone); sex hormones (e.g., anti-estrogens (tamoxifen, fulvestrant), aromatase inhibitors (anastrozole, letrozole), progestins (megestrol acetate), anti-androgens (bicalutamide, flutamide), and LHRH agonists (leuprolide, goserelin). Other chemotherapeutic agents include L-asparaginase and tretinoin, cyclophosphamide, or Cytoxan[®] (C) methotrexate (M), 5-flourouracil, or 5-FU (F), Adriamycin[®] (A) and Taxol[®] (T), prednisone 5-fluorouracil, capecitabine, methotrexate, gemcitabine, cytarabine (ara-C), and fludarabine.

Please amend the paragraph beginning on page 26, line 10 as follows:

Anti-diabetic agents include but are not limited to: (i) exogenously-administered insulin; (ii) agents that enhance insulin sensitivity (e.g., thiazolidinediones (e.g., rosiglitazone (AVANDIA[®]), pioglitazone (ACTOS[®]), troglitazone, and ciglitazone); and biguanides (e.g., metformin (GLUCOPHAGE[®]; GLUCOPHAGE[®] XR))); (iii) agents that enhance secretion of insulin (insulin secretagogues; e.g., sulphonylureas, such as gliclazide, tolbutamide, glimepiride, glibenclamide, tolazamide, and repaglinide; meglitinides; imidazolines such as efaroxan; and rapid-acting insulin secretagogues (e.g., nateglinide and repaglinide); and alpha-glucosidase inhibitors (e.g., acarbose (PRECOSE[®]), miglitol (GLYSET[®]))).

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Please amend the paragraph beginning on page 36, line 5 as follows:

Total RNA was extracted and purified with the Qiagen RNeasy kit (Qiagen, San Diego, CA). Five micrograms of total RNA was used in the first-strand cDNA synthesis with T7-d(T)₂₄ primer (GGCCAGTGAATTGTAATACGACTCACTATAGGGAGGC GG- (dT)₂₄) (SEQ ID NO: 1) and Superscript II (GIBCO-BRL, Rockville, MD). The second-strand cDNA synthesis was carried out at 16°C by adding *Escherichia coli* DNA ligase, *E. coli* DNA polymerase I, and RNase H to the reaction, followed by T4 DNA polymerase to blunt the ends of newly synthesized cDNA. The cDNA was purified through phenol/chloroform and ethanol precipitation. Using the BioArray High Yield RNA Transcript Labeling Kit (Enzo Diagnostics, Farmingdale, NY), the purified cDNA was incubated at 37°C for 5 h in an *in vitro* transcription reaction to produce cRNA labeled with biotin. cRNA (20 ug) was fragmented by incubating in a buffer containing 200 mM Tris-acetate (pH 8.1), 500 mM KOAc, and 150 mM MgOAc at 94°C for 35 min. The hybridization cocktail containing 15 µg adjusted fragmented cRNA mixed with Eukaryotic Hybridization controls (contains control cRNA and oligonucleotide B2) was hybridized with a pre-equilibrated human U133A Affymetrix chip at 45°C for 16 h. After the hybridization cocktails were removed, the chips were washed in a fluidic station with low-stringency buffer (6 X standard saline phosphate with EDTA, 0.01% Tween 20™ (Polysorbate), and 0.005% antifoam) for 10 cycles (two mixes/cycle) and high stringency buffer (100 mM N-morpholino-ethanesulfonic acid (MES), 0.1 M NaCl, and 0.01% Tween 20™ (Polysorbate)) for four cycles (15 mixes/cycle) and stained with SAPE (streptavidin phycoerythrin). This process was followed by incubation with normal goat IgG and biotinylated mouse anti-streptavidin antibody and restaining with SAPE. The chips were scanned in an HP ChipScanner (Affymetrix Inc, Santa Clara, CA) to detect hybridization signals. Scanned image output files were visually examined for major chip defects and hybridization artifacts and then analyzed with Affymetrix GeneChip® (array) Microarray Analysis Suite 5.0 software (Affymetrix). The image from each GeneChip® (array) was scaled such that the average intensity value for all arrays was adjusted to a target intensity of 150. The expression analysis files created by GeneChip® (array) Microarray Analysis Suite 5.0 software were exported as flat text files to Microsoft Excel and used for further analysis. Data analysis was performed to identify signals that were at least two-fold different between IGF-1 R inhibitor-treated samples and their respective controls.

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These results were screened for p-values less than 0.0025 in Student's t test, to identify transcripts that were induced or repressed. For hierarchical clustering analysis, data were imported into the Gene Cluster and TreeView software (Stanford University, Stanford, CA). Additional softwares used for data mining include GeneSpring 5. 0 (Silicon Genetics). Data were visualized using the Rainbow program (developed by Charles Bailey and Towia Libermann) that enables representation of data in color format according to their values on a logarithmic scale and with DNA-Chip Analyzer (dChip) 3, ~~which is freely available to academic users at www.dchip.org~~. Annotations and informations for all genes were retrieved using the NetAffx website (Affymetrix) and UnChip (Alberto Riva, Atul Butte, and Isaac Kohane; Childrens Hospital, Boston) and added to the data file. Annotated data were sorted according to functional relationships.